In the Specification

On page 1, please replace the first paragraph with the following:

Related Application

This is a §371 of PCT/JP2003/008751, with an international filing date of July 10, 2003 (WO 2004/007503 A1, published January 22, 2004), which is based on JP 2002-202657, filed July 11, 2002.

Technical Field

The present invention relates to therapeutic or prophylactic agents for preventing nausea and vomiting. Particularly, the present invention relates to therapeutic or prophylactic agents for preventing nausea and vomiting caused by μ-opioid agonists represented by morphine.

Please replace the paragraph spanning pages 1 and 2 with the following:

Background ~~Art~~

Nausea and vomiting, caused by administration of emetic drugs such as opioid analgesics and anticancer drugs, are one of the most suffering side effects for patients. In particular, morphine, which is generally used as an analgesic for patients suffering from cancer pain[[s]], is known to frequently cause nausea and vomiting as adverse side effects. D_2 antagonists such as domperidone and haloperidol or anti-emetic drugs including 5-HT_3 antagonists are used for preventing nausea and vomiting due to morphine, but the anti-emetic effect of these drugs is not clear. In particular, in the early stage of morphine administration, the dosage is not sufficient to relieve the pain in many cases because of nausea and vomiting induced by morphine. This is one of the factors that make the quality of life (QOL) of patients worse. 5-HT_3 antagonists are known to exhibit a remarkable anti-emetic effect against anticancer drugs and are generally used now. However, the following problem has recently been found: The 5-HT_3 antagonists exhibit a poor effect against delayed vomiting that

occurs over two or several days after the administration of the anticancer drugs. Recently, therapeutic effects of tachykinin antagonists for preventing nausea and vomiting have been reported, but they are not yet being used in practice. There is presently a demand for excellent therapeutic or prophylactic agents for preventing nausea and vomiting.

Please replace the paragraph spanning pages 2 and 3 with the following:

There are practically no reports on the anti-emetic effects of δ-antagonists, but the possibility of δ-antagonists as anti-emetic agents is suggested in some literature[[s]] (for example, Eur. J. Pharmacol. 128, 143-150, (1986), US Patent Nos. 5,681,830, 5,574,159, and 5,552,404, and Lancet 1, 714-716, (1982)). On the other hand, some reports refute the anti-emetic effects of δ-antagonists (for example, Biull. Eskp. Biol. Med. 103, 586-588, (1987). This publication reports that δ-antagonist ICI-154129 cannot inhibit vomiting due to morphine.) Consequently, not all of the δ-antagonists have anti-emetic effects. There also are reports that both the μ- and δ-receptors are involved in the anti-emetic effects (for example, Biull. Eskp. Biol. Med. 103, 586-588, (1987)). Therefore, useful anti-emetic compounds may be superior to μ- and δ-antagonistic balance. However, a prediction as to whether a particular compound has such an effect is difficult. Consequently, actual synthesis and evaluation of the compound are necessary.

Please replace the paragraph spanning pages 4 and 5 with the following:

~~Disclosure~~Summary of the Invention

~~It is an object of the present~~The invention ~~to~~ provides a therapeutic or prophylactic agent which can be widely used for preventing nausea and vomiting due to an emetic drug administration. In particular, ~~it is an object of~~ the ~~present~~ invention ~~to~~ provides a therapeutic or prophylactic agent for prevent nausea and vomiting due to μ-agonists represented by morphine.

Please replace the paragraph spanning pages 8 and 9 with the following:

~~Best Mode for Carrying Out the Invention~~Detailed Description

In embodiments according to the present invention, compounds represented by General Formula (I) are preferably used. In particular, preferable substituents of the compounds represented by General Formula (I) are as follows:

R^1 preferably represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 3 to 7 carbon atoms, a furanylalkyl group (where the alkyl moiety has 1 to 5 carbon atoms), or a thiophenylalkyl group (where the alkyl moiety has 1 to 5 carbon atoms);~~,~~ more preferably represents a cycloalkylalkyl group having 4 to 7 carbon atoms or an alkenyl group having 3 to 7 carbon atoms. Specifically, a cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, allyl, or butenyl group is preferable. Among them, a cyclopropylmethyl or allyl group is most preferable.